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(54) Title: ORAL COMPOSITIONS CONTAINING ANTIPLAQUE, ANTICALCULUS AGENTS

(57) Abstract

This invention involves oral-care compositions, comprising: (a) zinc oxide or zinc nitrate; a source of citrate ions; and one or more phosphorous-containing anticalculus agents selected from the group consisting of pyrophosphate, phosphonate, diphosphonate and pharmaceutically-acceptable linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)}^{(n+2)-}$ wherein n is an integer from 2 to 21; wherein the molar ratio of the zinc ions:citrate ions if from about 1.01 to about 1:20; the molar ratio of the zinc ions:phosphorus-containing anticalculus agents is from about 1:1 to about 1:20; and (b) a pharmaceutically-acceptable topical oral carrier. This invention also involves methods for treating or preventing dental plaque, calculus, gingivitis, or malodor of the oral cavity comprising amdinistering to the oral cavity of a human or other animal a safe and effective amount of such compositions.

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ORAL COMPOSITIONS CONTAINING ANTIPLAQUE, ANTICALCULUS AGENTS

This invention relates to oral compositions, such as dentifrices and oral solutions, for the treatment or prevention of dental plaque, calculus, gingivitis, and mouth malodor.

Background of the Invention

The mouth is a habitat for microbial growth and colonization. Within the mouth, the gums, lips, oral mucosa (cheek), palate, tongue and teeth provide surfaces for the colonization and accumulation of bacteria. Teeth are unique in the oral cavity because they have hard, non-shedding surfaces where bacteria and their products (dental plaque) can significantly accumulate, especially in approximal areas and along the gingival crevice.

Dental plaque is a rough sticky film on the teeth that is made up of saliva, bacteria and food particles which adheres tenaciously to teeth at points of irregularity or discontinuity. Within a few hours of teeth cleaning, a film of salivary mucins, consisting primarily of proteins, forms on the teeth. Various oral bacteria colonize the mucins and multiply, forming a layer of plaque. Carbohydrate food debris adheres to the mucins and is digested by some types of plaque-causing bacteria. The digestion produces both by-products which add to the plaque, and produces acid which erodes tooth enamel. The bacterial by-products produced in the oral cavity also include foul smelling gases which can result in malodor of the oral cavity.

If not prevented or removed, plaque may become embedded with mineral salts, containing calcium and phosphate, to form a hard crusty deposit, calculus or tartar, on the teeth. Calculus may be white or yellowish in color or may be stained or discolored by extraneous agents. Calculus tends to be more unsightly than plaque and much more difficult to remove from the teeth. The toxins in plaque and calculus can irritate the gingival tissues surrounding the coated teeth,

causing inflammation and destruction of the gums which can lead to other complications.

Zinc is an anticalculus agent; however, compositions containing zinc generally taste astringent and unpleasantly bitter. Like the chemical and biological activities, the negative aesthetics of the zinc cation are dose dependent: higher concentrations of zinc exhibit poorer aesthetics; therefore, increasing the concentration of free zinc tends to increase efficacy at the expense of aesthetics. This coupled behavior between efficacy and aesthetics has limited the utility of zinc in oral compositions. Pyrophosphate is also an anticalculus agent and, likewise, has an unpleasant taste which worsens with increased pyrophosphate concentration. By carefully formulating zinc and pyrophosphate-containing compositions, it has been surprisingly found that the level of zinc in an oral composition can be increased, thus increasing the corresponding anticalculus effect, without greatly increasing the negative aesthetics of the composition. Applicants have surprisingly found that certain ratios of zinc:citrate:pyrophosphate in combination with certain formulation components unexpectedly provide oral compositions which are stable for longer time periods than are other formulations.

Summary of the Invention

This invention involves oral-care compositions comprising:

(a) zinc oxide or zinc nitrate; a source of citrate ions; and one or more phosphorus-containing anticalculus agents selected from the group consisting of pyrophosphate, phosphonate, diphosphonate and pharmaceutically-acceptable linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21;

wherein a molar ratio of the zinc ions:citrate ions is from about 1:0.1 to about 1:20; the molar ratio of the zinc ions:phosphorus-containing anticalculus agents is from about 1:1 to about 1:20; and

(b) the pharmaceutically-acceptable topical oral carrier.

Detailed Disclosure of the Invention

This invention provides compositions effective against dental plaque formation, calculus formation, gingivitis, and mouth malodor. Such compositions comprise certain zinc salts and certain molar ratio amounts of citrate and pyro relative to zinc in a pharmaceutically-acceptable carrier.

"Pyro", as used herein, refers to pyrophosphate; phosphonate; diphosphonate; and pharmaceutically-acceptable polyphosphates including, but not limited to, linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21.

"Pharmaceutically-acceptable topical oral carrier", as used herein, denotes a carrier for the active compounds of this invention (hereinafter "Actives") comprising solid or liquid filler diluents suitable for use in contact with the oral tissues of humans and other animals without undue toxicity, incompatibility, instability, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. Such topical oral carrier, when combined with Actives of this invention, results in a composition which is administered topically to the oral cavity. Preferably such compositions are held in the oral cavity for a period of time, and then largely expectorated rather than being swallowed. Such compositions include mouthwashes, mouth rinses, mouth sprays, dental treatment solutions, toothpastes, liquid dentifrices and the like and are more fully described hereinafter. Dentifrices and mouthwashes are the preferred compositions.

"Free pyro", as used herein, refers to pyro that is not bound or chelated to the transition metal, zinc.

"Free zinc", as used herein, refers to hydrated zinc cationic species, such as $Zn(H_2O)_6^{2+}$.

"Safe and effective amount" as used herein means an amount of compound or composition sufficient to induce a significant positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the compound or composition will vary with the particular condition being treated, the age and physical condition of the patient being

treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed, the particular pharmaceutically-acceptable carrier utilized, and like factors.

The term "comprising", as used herein, means that various additional components can be conjointly employed in the compositions of this invention.

As used herein, percentages listed are weight percentage of composition unless otherwise specified.

Zinc:Citrate and Zinc:Pyro Ratios

The amounts of pyro and citrate are expressed in terms of a ratio to the amount of zinc in the oral composition. On a molar basis, the amount of citrate relative to zinc is at least 0.1 when the amount of zinc is "1" (*i.e.* the ratio of zinc:citrate is at most 1:0.1). Likewise, the amount of pyro relative to to the amount of zinc is at least 1 when zinc is 1 (*i.e.* the ratio of zinc:pyro is at most 1:1). Preferred zinc:citrate ratios are from about 1:0.1 to about 1:20, more preferably from about 1:0.5 to about 1:4, more preferably from about 1:1 to about 1:3. Preferred zinc:pyro ratios are from about 1:1 to about 1:20, more preferably from about 1:2 to about 1:6, more preferably from about 1:3 to about 1:5. Also preferred is a zinc:citrate:pyro ratio wherein the sum of the ratio amounts of citrate and pyro is from about 3 to about 9, more preferably from about 4 to about 7, when the ratio amount of zinc is 1.

The amount of zinc suitable for the purposes of this invention is from about 0.005% to about 5% Zn; more preferably from about 0.05% to about 2% Zn; more preferably still from about 0.1% to about 0.6% Zn. In dentifrice compositions, the preferred amounts of zinc are from about 0.1% to about 2%, more preferably from about 0.3% to about 0.6%. In mouthwashes, mouth rinses, mouth sprays and dental solutions, the preferred amount of zinc is from about 0.005% to about 1%, more preferably from about 0.01% to about 0.75%, more preferably still from about 0.05% to about 0.5%.

The amount of citrate anion suitable for the purposes of this invention is from about 0.015% to about 15% citrate. In dentifrice compositions, the preferred amounts of citrate anion are from about

0.2 % to about 8%, more preferably from about 0.4% to about 7%, more preferably still from about 0.6% to about 6%. In mouthwashes, mouth rinses, mouth sprays and dental solutions, the preferred amount of citrate anion is from about 0.01% to about 12%, more preferably from about 0.1% to about 6%, more preferably still from about 0.15% to about 1%.

The amount of pyro anion suitable for the purposes of this invention is from about 0.5% to about 15% pyro. In dentifrice compositions, the preferred amounts of pyro ion are from about 1% to about 9%, more preferably from about 2.5% to about 5%. In mouthwashes, mouth rinses, mouth sprays and dental solutions, the preferred amount of pyro anion is from about 0.01% to about 25%, more preferably from about 0.1% to about 5%.

Suitable sources of zinc ions include zinc oxide and $Zn(NO_3)_2$. Zinc sources that are not suitable are zinc ethylenediaminetetraacetate (ZnEDTA) and zinc nitrilotriacetate (ZnNTA). The preferred source of zinc ions is ZnO.

Suitable sources of citrate ions include citric acid; alkali metal salts of citric acid, especially sodium citrate and potassium citrate; pharmaceutically acceptable hydrated and dehydrated salts of any of the above; and mixtures of any of the above.

Suitable sources of pyro ions are disclosed in U.S. Pat. No. 4,885,155, issued December 5, 1989 to Parran & Sakkab; U.S. Pat. No. 3,678,154, issued July 18, 1972 to Widder *et al.*; U.S. Pat. No. 3,737,522, issued June 5, 1973 to Francis *et al.*; and U.S. Pat. No. 4,627,977, issued December 9, 1986 to Gaffar *et al.*; each is incorporated herein by reference. Suitable pyro ion sources include tetrasodium pyrophosphate, sodium acid pyrophosphate ($Na_2H_2P_2O_7$), tetrapotassium pyrophosphate ($K_4P_2O_7$); phosphates including, but not limited to, linear condensed polyphosphates of the general formula: $M_{(n+2)}P_nO_{(3n+1)}$ wherein M is Na or K, and n is an integer from 2 to 21; phosphonates and diphosphonates, such as EHDP (ethane-1-hydroxy-1,1-diphosphonate) and AHP (azacycloheptane-2,2-diphosphonic acid); pharmaceutically-acceptable alkali metal salts of pyrophosphates, polyphosphates, phosphonates and diphosphonates; and mixtures of any of the above. Preferred

polyphosphate ions are those of the above formula wherein n is 6, 13, and 21. Preferred pyro ions are pyrophosphate ions. Preferred alkali metals are sodium and potassium; mixtures of alkali metal salts are acceptable. A more preferred source of pyro ions is a potassium salt of the pyro ion.

Compositions

Components of the topical, oral carrier are suitable for administration to the oral cavity of a human or other animal and are compatible with one another and the other components, especially with the Actives, used in an oral composition of this invention. The term "compatible" as used herein, means that the components are capable of being co-mingled with one another, in a manner such that there is no interaction which would substantially reduce the efficacy of the oral composition under ordinary use conditions.

Preferred topical, oral carriers provide the desired characteristics for mouthwashes, mouth rinses, mouth sprays, dental treatment solutions, toothpastes, dental gels, toothpowders, prophylaxis pastes, and the like. The topical, oral carriers of this invention comprise components typically used in such compositions which are well known to a skilled practitioner. Such components include, but are not limited to, anticaries agents, antiplaque agents, anticalculus agents, dental abrasives, surfactants, flavoring agents, sweetening agents, binders, humectants, thickening agents, buffering agents, preservatives, coloring agents and pigments, ethanol and water.

The pH of oral compositions of this invention is critical but can be varied to some extent. The compositions must be at a pH which is safe for contact with the tissues of the oral cavity, *i.e.* below a pH of about 9 for humans, preferably below a pH of about 8.5. Otherwise, the pH of the compositions is preferably above pH 6, more preferably above pH 7, more preferably still, above pH 7.5.

During manufacture of a composition of this invention, the conditions for addition of each component should be optimized such that the pH of the mixture does not drop below formulation pH at any time during mixing of the ingredients. To optimize stability of the final

composition a pH of at least about 7.5 should be maintained at all times.

Water is a component of the topical, oral carriers of the compositions of the subject invention. Water employed in the preparation of the commercially suitable compositions should preferably be of low ion content and free of organic impurities. Water preferably comprises from about 2% to about 99%, more preferably from about 20% to about 95% of the compositions of the subject invention. When in the form of toothpaste, the compositions preferably comprise from about 20% to about 99.5%, more preferably from about 30% to about 99%, still more preferably from about 35% to about 98%, more preferably still from about 40% to about 97% water. Mouthwashes comprise preferably from about 2% to about 99.5%, more preferably from about 45% to about 99%, more preferably still from about 75% to about 98%, water.

In preparing oral compositions of this invention, it is desirable to add binders and/or thickening agents, particularly to toothpaste compositions to provide a desired consistency. Suitable binders for these compositions are those which are non-ionic at the formulation pH of the composition. By "non-ionic" is meant, not more than about 10% ionized. As used herein "formulation pH" means the pH of the final composition. Suitable binders include, but are not limited to, natural gums such as gum karaya, gum arabic, and gum tragacanth; polysaccharide gums such as xanthan gum; and other natural products such as carrageenan; chemically modified natural products such as those based on cellulose esters, that is, carboxylmethylcellulose (CMC), hydroxyethylcellulose (HEC), and hydroxypropylcellulose (HPC); and synthetic binders such as polyvinylpyrrolidone; and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Carboxyvinyl polymer binders are less desirable, but may be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Blends and mixtures of the suitable binders may significantly improve the characteristics of compositions made therewith. Preferred binders are chemically modified celluloses such

as CMC or HEC; more preferred is HEC. Binders and thickening agents are generally present in the compositions of this invention in combined amounts of from about 0.1% to 10%, preferably from about 0.25% to about 7.5%, more preferably from about 0.5% to about 3.5%.

Optional Components

Dental abrasives useful in the topical, oral carriers of the compositions of this invention include many different materials. The material selected must be one which is compatible with the composition of interest and does not excessively abrade dentin. These include, for example, silicas, including gels and precipitates, calcium carbonate, dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, calcium polymeta-phosphate, insoluble sodium polymeta-phosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and other materials such as those disclosed by Cooley *et al.* in U.S. Pat. No. 3,070,510, issued December 25, 1962, incorporated herein by reference. Mixtures of abrasives may also be used.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. For this reason they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 and 30 microns, preferably between about 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in U.S. Pat. No. 3,538,230, issued March 2, 1970 to Pader *et al.*, and in U.S. Pat. No. 3,862,307, issued June 21, 1975 to DiGiulio, both incorporated herein by reference. Preferred are the silica xerogels marketed under the tradename Syloid® by the W.R. Grace & Company, Davidson Chemical Division. Preferred precipitated silica materials include those marketed by the J. M. Huber Corporation under the tradename, Zeodent®, particularly the silica carrying the designation Zeodent 119®. These silica abrasives are described in U.S. Pat. No.

4,340,583, Wason, issued July 20, 1982, incorporated herein by reference.

Mixtures of abrasives may be used. The amount of abrasive in the compositions described herein ranges from about 6% to about 70%, preferably from about 15% to about 50%, more preferably from about 15% to about 30%, when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a tooth powder.

Flavoring agents can also be added to the oral compositions of this invention to make them more palatable. Suitable flavoring agents include menthol, oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of clove. Flavoring agents are generally included in the subject compositions in amounts of from 0% to about 3%, preferably from about 0.04% to about 2% by weight.

Coloring agents may be added to compositions of this invention to improve appearance. If present, coloring agents typically are included at levels of from about 0.001% to about 0.5% by weight.

Sweetening agents are also preferred in the compositions of this invention to make them more palatable. Sweetening agents which can be used include aspartame, acesulfame, saccharin salts, dextrose, glucose, levulose thaumatin, D-tryptophan, dihydrochalcones, and cyclamate salts. Saccharin salts are preferred. Sweetening agents are generally used in the subject compositions in amounts of from 0% to about 6%, preferably from about 0.005% to about 5% by weight.

Oral compositions can also contain a surfactant. Suitable surfactants are those which are reasonably stable and form suds throughout the pH range suitable for compositions of this invention, including nonsoap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents, and compatible mixtures thereof. Many of these suitable surfactants are disclosed in U.S. Pat. No. 4,051,234, issued to Gieske *et al.* on September 27, 1977, and in U.S. Pat. No. 3,959,458 issued to Agricola, Briner, Granger and Widder on May 25, 1976, both of which are incorporated herein by reference. Surfactants are typically present in compositions of this invention at a level of from 0% to about 20%, preferably from about

0.1, more preferably from about 1% to about 4% by weight. Surfactants may also be used as solubilizing agents to help retain sparingly soluble components, e.g., some flavoring agents, in solutions. Surfactants suitable for this purpose include polysorbates and poloxamers.

Another optional component of the oral carriers of the compositions of this invention is a humectant. The humectant serves to keep toothpaste compositions from hardening upon exposure to air, and to give mouthwash and toothpaste compositions a moist feel to the mouth. Certain humectants can also impart desirable sweetness of flavor to mouthwash and toothpaste compositions. The humectant, on a pure humectant basis, generally comprises from 0% to about 70%, preferably from about 2% to about 55%, by weight of the compositions herein. Suitable humectants for use in compositions of this invention include edible polyhydric alcohols such as glycerin, sorbitol, xylitol, polyethylene glycol, and propylene glycol, especially sorbitol and glycerin. Preferred humectants are sorbitol and glycerin; more preferred is sorbitol.

Opacifiers may also be used in toothpastes of this invention to render the toothpaste opaque. Suitable opacifiers include titanium dioxide and some abrasives including, for example, magnesium aluminum silicate. Opacifiers generally comprise from 0% to about 4%, preferably from about 0.5% to about 3% by weight of the compositions herein.

Other optional components of the compositions of this invention are preservatives. The preservatives prevent microbial growth in the compositions. Suitable preservatives include methylparaben, propylparaben, benzoates and ethanol. If the preservative is ethanol, it generally comprises from 0% to about 35% by weight, preferably from about 5% to about 15%, of the compositions herein. Other preservatives generally comprise from 0% to about 5% by weight, preferably from about 0.08% to about 2%, of the compositions herein.

Antimicrobial, antiplaque agents can also optionally be present in the oral compositions of this invention, on the condition that they are compatible with the Actives. Such agents may include, but are not limited to, triclosan, 2,4,4'-trichloro-2'-hydroxydiphenyl ether, as

described The Merck Index, 11th Ed. (1989), p. 1520 (entry No. 9573); chlorhexidine, (Merck Index, No. 2090); alexidine (Merck Index, No. 222); hexetidine (Merck Index, No. 4624); sanguinarine (Merck Index, No. 8320); benzalkonium chloride (Merck Index, No. 1066); salicylanilide (Merck Index, No. 8299); domiphen bromide (Merck Index, No. 3411); cetylpyridinium chloride, (CPC) (Merck Index, No. 2024); tetradecylpyridinium chloride, (TPC); N-tetradecyl-4-ethylpyridinium chloride (TDEPC); octenidine; delmopinol, octapinol, and other piperidino derivatives; nicin preparations; antibiotics such as augmentin, amoxicillin, tetracycline, doxycycline, minocycline, and metronidazole; and peroxides, such as cylium peroxide, hydrogen peroxide, and magnesium monoperthalate and its analogs as described in U.S. Patent No. 4,670,252; and analogs and salts of the above antimicrobial antiplaque agents. If present, the antimicrobial antiplaque agents may comprise from 0% to about 6%, preferably from about 0.1% to about 5% by weight of the compositions of this invention.

Bleaching agents can also be present in the oral compositions of this invention. Suitable bleaching agents include organic and inorganic oxidizing agents such as hydrogen peroxide, alkali metal peroxides and superoxide and organic peroxides such as monoperoxyphthalates and perbenzoic derivatives. If present, such bleaching agents may comprise from 0% to about 6%, preferably from about 1% to about 5% by weight of the compositions of this invention.

Nutrients can also be present in the oral composition of this invention, on condition that they are compatible with the Actives. Such agents may include folate, retinoids (Vitamin A), Vitamin C, Vitamin E. If present, the nutrients generally comprise from about 0.001% to about 10% by weight of the compositions of this invention.

Other optional ingredients include a safe and effective amount of a fluoride ion source, which typically is in the form of a water-soluble fluoride compound. This water-soluble fluoride compound is typically present in the compositions of this invention in an amount sufficient to give a fluoride concentration of from about 0.0025% to about 5.0% by weight, preferably from about 0.005% to about 2.0% by weight. Preferred fluoride sources are sodium fluoride,

acidulated phosphate fluoride, and sodium monofluorophosphate. U.S. Pat. No. 3,678,154, issued July 18, 1972 to Widder *et al.*, discloses such salts as well as others, and is incorporated herein by reference.

Other optional ingredients include synthetic or natural anionic polymeric polycarboxylates, polysaccharides, and polysulfates. The polymers may be present at a weight amount of from about 0.05% to about 3%, more preferably form about 0.05% to about 2%, more preferably still from about 0.1% to about 2%. Suitable polymers include but are not limited to copolmers of maleic acid anhydride or acid with another polymerizable ethylenically unsaturated monomers, linear polycarboxylates, alginates, pectins, carageenans. Most preferred are 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether (methoyethylene) having a molcular weight (M.W.) of about 30,000 to about 1,000,000. These copolymers are available for example as Gantrez® AN 139 (M.W. 500,000), A.N. 119 (M.W. 250,000) and preferably S-97 Pharmaceutical Grade (M.W. 70,000), of GAF Corporation.

Other operative polymeric polycarboxylates include those disclosed in U.S. Pat. No. 3,956,480, such as the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone, or ethylene, the latter being available for example as Monsanto EMA No. 1103, M.W. 10,000, and EMA Grade 61, and 1:1 copolymers of acrylic acid with methyl or hydroxyethyl methacrylate, methyl or ethyl acrylate, isobutyl vinyl ether or N-vinyl 2-pyrrolidone.

Preferred Compositions

Preferred compositions of this invention are in the form of dentifrices, especially toothpastes. Components of toothpastes generally include a dental abrasive (from about 10% to about 50%), a surfactant (from about 0.5% to about 10%), a thickening agent (from about 0.1% to about 5%), a humectant (from about 10% to about 70%), a flavoring agent (from about 0.04% to about 2%), a sweetening agent (from about 0.1% to about 3%), a coloring agent (from about 0.01% to about 0.5%) and water (from about 2% to about 45%).

Other preferred compositions of this invention are mouthwashes, mouth sprays, and dental solutions. Components of such mouthwashes and mouth sprays include water (from about 45% to about 99%), ethanol (from 0% to about 25%), humectant (from 0% to about 50%), surfactant (from about 0.01% to about 7%), flavoring agent (from about 0.04% to about 2%), sweetening agent (from about 0.1% to about 3%), and coloring agent (from about 0.001% to about 0.5%). Such mouthwashes and mouth sprays may also include an antiplaque agent (from about 0.1% to about 5%).

Methods of Use

Another aspect of this invention involves methods of treating or preventing mouth odor, dental plaque, calculus and gingivitis, by application of compositions comprising a safe and effective amount of Actives, to tissues of the oral cavity. Such compositions are described hereinabove.

These methods involve administering a safe and effective amount of Actives, preferably by administering an oral composition of this invention, as described hereinabove, to the oral cavity. Preferably methods of this invention comprise administering an amount of composition comprising at least about 0.001g of the Actives. The teeth and other oral cavity tissues are exposed to the Actives.

When the oral composition is a toothpaste, preferably from about 0.3 grams to about 15 grams, preferably from about 0.5 grams to about 5 grams, more preferably from about 1 to about 2 grams, of toothpaste is applied to an applicating device e.g., a toothbrush. The applicating device is then contacted with the oral cavity surfaces in a manner such that the oral composition is contacted with tissue of the oral cavity, especially the teeth and gums. The applicating device may be further used to effect an even distribution of the oral composition to the tooth surface, for example by brushing. The application preferably lasts for a period of from about 15 seconds to about 10 minutes, more preferably from about 30 seconds to about 3 minutes, more preferably still from about 1 minute to about 2 minutes. Following application, the toothpaste residue is typically removed from the tooth surface by using a liquid acceptable to the oral cavity, typically water, to rinse and be expectorated from the oral cavity.

When the oral composition is a mouthwash, typically from about 1 ml. to about 20 ml., preferably from about 2 ml. to about 15 ml., most preferably from about 10 ml. to about 15 ml., of liquid mouthwash containing the antiplaque Active is introduced to the oral cavity. The liquid mouthwash is then agitated for from about 10 seconds to about 10 min., preferably from about 15 seconds to about 3 min., more preferably from about 30 seconds to about 2 minutes, within the oral cavity to obtain an improved distribution of the mouthwash over the tissue of the oral cavity. Following agitation, the mouthwash is typically expectorated from the oral cavity.

Application frequency is preferably from about 3 times weekly to about 4 times daily, more preferably from about once daily to about 3 times daily, more preferably still from about once to about twice daily. The period of treatment typically ranges from about one day to a lifetime.

Examples

The following non-limiting examples further describe and demonstrate preferred embodiments within the scope of this invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations are possible without departing from the spirit and scope of this invention.

The compositions of this invention can be made using methods which are commonly used to produce oral care products.

EXAMPLES I-VI

The following are examples of dentifrice compositions of this invention and are made using conventional processes. The numbers listed are weight percentages of the compositions. During manufacture, the pH is maintained at a minimum of pH 7.5.

Ingredient	Ex. I	Ex. II	Ex. III	Ex. IV	Ex. V	Ex. VI
Sorbitol	31.65	31.65	31.65	31.65	31.65	31.65
PEG-6		3	3	3	3	3
Citric Acid	1.46	0.088	0.91	0.433	1.05	0.44
Sodium Citrate	3.68		0.144	0.856		5.28
Zinc Nitrate	2.97					
Zinc Oxide		0.374	0.407	0.407	0.407	0.407
Tetrapotassium Pyrophosphate (annhydrous)	7.12	7.58			5.78	
Sodium Acid Pyrophosphate				0.62		0.497

Tetrasodium Pyrophosphate			6.65	4.6		3.39
Sodium Fluoride	0.24	0.24	0.24	0.24	0.24	0.24
Sodium Saccharin	0.46	0.46	0.46	0.46	0.46	0.46
Titanium Dioxide	0.5	0.5	0.5	0.5	0.5	0.5
Silica	22	22	22	22	22	22
Glycerin	9	9	2.25	2.25	9	2.25
Carboxymethylcellulose	1		0.5	0.75	0.5	0.5
Xanthan Gum		0.4	0.4	0.75	0.4	0.4
Hydroxyethylcellulose		0.5				
Sodium Lauryl Sulfate (27.9% Aqueous solution)	4	4	4	4	4	4
Flavor	1.1	1.1	1.1	1.1	1.1	1.1
KOH/HCl/water	q.s. to pH 7.5	q.s. to pH 8.5	q.s. to pH 8.0	q.s. to pH 8.0	q.s. to pH 8.0	q.s. to pH 8.0
TOTAL	100	100	100	100	100	100

EXAMPLE VII

Following dental prophylaxis, a person brushes his teeth for sixty seconds twice daily using 1 g of a fluoride, non-anticalculus toothpaste. After eight weeks he receives dental prophylaxis performed by his dentist. For the following eight weeks the person brushes his teeth for sixty seconds twice daily with 1 g of the composition of Example I. After eight weeks, the person has significantly less calculus on his teeth than he did after the first eight weeks.

EXAMPLE VIII

Following dental prophylaxis, a person brushes his teeth for sixty seconds twice daily using 1 g of a fluoride, non-anticalculus toothpaste. After one week he receives dental prophylaxis performed by his dentist. For the following week the person brushes his teeth for sixty seconds twice daily with 1 g of the composition of Example IV. After one week, the person has significantly less plaque on his teeth than he did after the first week.

EXAMPLE IX

Following dental prophylaxis, a person brushes his teeth for sixty seconds twice daily using 1.5 g of a fluoride, non-anticalculus toothpaste. After nine weeks he receives dental prophylaxis performed by his dentist. For the following nine weeks the person brushes his teeth for sixty seconds twice daily with 1.5 g of the composition of Example III. After nine weeks, the person has

significantly less calculus on his teeth than he did after the first nine weeks.

EXAMPLES X-XIV

The following are examples of mouthwash and dental rinse compositions of this invention and are made using conventinal processes. The amounts listed are weight percentages of the compositions. During manufacture, the pH of the following compositions is maintained at a minimum of pH 7.5.

Component	Ex. X	Ex. XI	Ex. XII	Ex. XIII	Ex. XIV
Glycerin	10	10	10	10	10
Ethanol	10	10	10	10	10
Sodium Citrate	0.41	3.84			1.28
Citric Acid			11.4	3.8	
Zinc Chloride		1.36			
Zinc Oxide	0.081		1.63	0.81	0.41
Tetrapotassium Pyrophosphate (60% Sol'n)	1.1			5.51	1.1
Tetrasodium Pyrophosphate				2.66	0.27
Sodium Tripolyphosphate			7.36		0.37
Sodium Acid Pyrophosphate		6.66			0.22
Sodium Lauryl Sulfate	0.4	0.4	0.4	0.4	0.4
Sodium Saccharin	0.03	0.03	0.03	0.03	0.03
Flavor	0.22	0.22	0.22	0.22	0.22
NaOH/HCL & Water	q.s. 100% at pH 7.5	q.s. 100% at pH 8.5	q.s. 100% at pH 8.5	q.s. 100% at pH 7.5	q.s. 100% at pH 8.0

EXAMPLE XV

Following dental prophylaxis, a person rinses her mouth for twenty seconds twice daily for a period of eight weeks using 10 ml of a non-anticalculus mouth rinse. After eight weeks, the person received dental prophylaxis and rinses for twenty seconds twice daily with 10 ml of the composition of Example XI. After eight weeks, the person has significantly less calculus on her teeth than she did after the first eight weeks, using the non-anticalculus mouth rinse.

EXAMPLE XVI

Following dental prophylaxis, a person rinses her mouth for thirty seconds twice daily for a period of one week using 12 ml of a non-antiplaque mouth rinse. During this week, the person does not brush her teeth. At the end of one week, the person received dental prophylaxis and rinses for thirty seconds twice daily with 12 ml of the composition of Example XIII. During this week, the person does not brush her teeth. At the end of one week, the person has significantly less plaque on her teeth than she did after the first week, using the non-antiplaque mouth rinse.

EXAMPLE XVII

Following dental prophylaxis, a person rinses her mouth for forty-five seconds twice daily for a period of nine weeks using 15 ml of a non-anticalculus mouth rinse. After nine weeks, the person received dental prophylaxis and rinses for forty-five seconds twice daily with 15 ml of the composition of Example XIV. After nine weeks, the person has significantly less calculus on her teeth than she did after the first nine weeks, using the non-anticalculus toothpaste.

While particular embodiments of this invention have been described, it will be obvious to those skilled in the art that various changes and modifications to these examples can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

Claims

1. An oral-care composition comprising:

a) (i) zinc oxide or zinc nitrate;

(ii) a source of citrate ions; and

(iii) one or more phosphorus-containing anticalculus agents selected from pyrophosphate, phosphonate, diphosphonate and pharmaceutically-acceptable linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21;

wherein the molar ratio of the zinc ions:citrate ions is from 1:0.1 to 1:20, preferably from 1:0.5 to 1:4, more preferably from 1:1 to 1:3; the molar ratio of the zinc ions:phosphorus-containing anticalculus agents is from 1:1 to 1:20, preferably from 1:1 to 1:6, more preferably from 1:3 to 1:5; and

(b) a pharmaceutically-acceptable topical oral carrier.

2. The composition of Claim 1 in the form of a dentifrice wherein the pharmaceutically acceptable topical oral carrier comprises a dental abrasive.

3. The composition of any of Claims 1-2 comprising a binder which is non-ionic at the formulation pH of the composition.

4. The composition of Claim 1 in the form of a solution selected from a mouthwash, a mouth rinse, a dental solution, and a mouth spray, wherein the pharmaceutical carrier comprises a material selected from a humectant, ethanol, and a nonionic surfactant.

5. The composition of any of Claims 1-4 wherein the pH of the composition is above pH 7; preferably above 7.5.

6. The composition of any of Claims 1-5 comprising from 0.01% to 0.75% zinc.

7. The composition of any of Claims 1-6 wherein the anticalculus agent is selected from pyrophosphate, EHDP, AHP, and linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is 6, 13, or 21, preferably the anticalculus agent is pyrophosphate, preferably a potassium salt of pyrophosphate.

8. The composition of any of Claims 1-7 comprising from 35% to 99.5 percent water.

9. The composition of any of Claims 1-8 comprising a source of fluoride ions yielding from 0.0025% to 5% by weight fluoride ions.

10. A method for treating or preventing dental plaque, calculus or malador of the oral cavity comprising administering to the oral cavity of a human or other mammal a safe and effective amount of a composition selected from Claims 1-9.

INTERNATIONAL SEARCH REPORT

Inter. ..onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/16 A61K33/42 A61K33/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 295 116 (UNILEVER) 14 December 1988 see examples 1-8	1-10
A	US,A,4 187 288 (CORDON ET AL.) 5 February 1980 see column 2, line 62 - column 3, line 1; claims 1,2	1-10
A	DE,A,27 47 852 (COLGATE-PALMOLIVE) 3 May 1979 see claims 1,3,13	1-10
A	EP,A,0 396 232 (VIPONT PHARMACEUTICAL INC.) 7 November 1990 see the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same pat.nt family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 1994	13. 04. 94

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 309 409 (COLL-PALAGOS ET AL.) 5 January 1982 see claim 1	1-10
A	US,A,5 000 944 (PRENCIPE ET AL.) 19 March 1991 see claim 1	1-10

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